CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-986

MEDICAL REVIEW(S)

1. Medical Officer Review:
1.1. Administrative Summary
1.1.1. NDA: #20986

1.1.2. Review: #1

1.1.3. Submissions
1.1.3.1. Paper submission: 9/15/99
1.1.3.2. CANDA submission: none
1.1.3.3. Major amendment: none
1.1.3.4. Supplemental submissions:
-10/8/98 Biopharm diskettes
-10/20/99 Biopharm diskettes
-11/16/98 Correction of listing for investigators and sites in Europe
-11/16/98 Actual submission of electronic data sets in SAS
-12/14/99 Correction of listing for investigators and sites in North America and in the NIDDM study
-1/14/99 Safety update
-2/26/99 Biopharm data
-3/8/99 Mixing information
-3/31/99 Information from the extension trial
-4/12/99 EXCEL spreadsheet of clinical data (incomplete)
-4/20/99 Assay validation
-5/7/99 QC data for Biopharm
-5/7/99 Assay precision data
-5/25/99 Information regarding lab handling of samples
-5/26/99 Information for Biopharm regarding the variability studies
-5/27/99 Draft patient labeling
-5/28/99 Draft patient labeling
-6/2/99 Errors in patient disposition and demographics-paper copies not valid
6 volumes
(provided to M.O. and Stats 8/10/99)
-6/3/99 Efficacy data on diskette-not formatted as requested- not linked to the hypoglycemia data
(provided to M.O. and Stats 8/2/99)
-6/8/99 Update on pregnancy outcome
-6/9/99 FAX indicating the location of the adverse event narratives
-6/10/99 Information on the number of patients treated outside protocol and outliers for clinical chemistry values. Did not include the number of patients on various treatment regimens; only included changes in regimens.
-6/16/99 Hypoglycemia information on diskette-not formatted as requested
-with discrepancies compared to the SAS data --
-6/29/99 Physician insert
-7/21/99 Draft package insert and carton on diskette
-8/5/99 Phase IV commitment for Biopharm

Signature + cc list is on pg 58.

-8/5/99 Pre-approval safety update #2
-8/10/99 Information on adverse events, but not different than what was previously available
Information on hypoglycemia-review already complete
Injection number and timing-for those who changed, not absolute values

1.1.4. Review completed: 8/13/99

1.2. Drug Name
1.2.1. Generic name: X-14; insulin aspart
1.2.2. Proposed trade name: NovoLog

1.3. Sponsor: Novo Nordisk Pharmaceuticals

1.4. Pharmacologic category: diabetic; insulin analogue

1.5. Proposed indications:

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1.6. Dosage form and route of administration:
1.6.1. Dosage form: vials for injection, pre-filled syringes, and cartridges for use in specified pens.
1.6.2. Dosage: to be titrated
1.6.3. Route of administration: subcutaneous injection from syringes and vials (10 ml)
(possible mixing)
subcutaneous injection from pre-filled syringes ——
3 ml syringes)
(unlikely mixing)
subcutaneous injection from pens (——3 ml cartridges)
(no mixing)

1.7. NDA drug classification: Standard

1.8. Important related drugs: insulin lispro
human insulin (semi-synthetic and recombinant)
animal insulins (bovine, porcine, and bovine-porcine mixtures)
insulin-like growth factors

1.9. Related reviews:
IND —— 6/8/99 Adverse events-hypoglycemia
7/13/99 Adverse events-hypoglycemia
7/16/99 Adverse event-hypoglycemia

7/21/99 Adverse event-pregnancy
8/11/99 Adverse event-pregnancy

1.10. Materials reviewed:

1.10.1. Volumes 1, 67-70, 82-84, 89, 93-95, 97
Safety updates
Preliminary extension information from North America

1.10.2. Division file records

1.10.3. Amendments

1.10.4. Investigator brochure

1.11. Table of Contents

2. Introduction

Excepting insulin lispro, in current U100 insulin preparations, the insulin molecule tends to aggregate as a hexamer. Dissociation must occur before insulin can be absorbed into the blood. Conversely, the insulin-like growth factor (IGF)-I monomer demonstrates a decreased propensity for aggregation. Although the two compounds share large regions of structural homology, there are non-homologous regions.

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The new molecular entity being considered in this NDA, X-14 (insulin aspart), is another insulin analogue with recombinant substitution of aspartate for proline at position 28 of the B-chain. Aspartate is an amino acid with polarity. The introduction of such intermolecular charge repulsion at the end of the B-chain reduced the tendency of the modified insulin to aggregate. Early studies confirmed that the modified insulin tended to lower glucose earlier than human regular insulin when given by subcutaneous injection. Although the sponsor has not compared differences in the onset of action between X-14 and human regular insulin in humans when given via ———————— it is presumed that the rapidity of action onset observed with X-14 is related to its rate of absorption through the skin and not to alterations in binding to and activation of the insulin receptor. This more rapid absorption permits administration closer to mealtime and somewhat reduces the need for advanced planning of food intake. It was also hoped that the shorter duration of action would result in less hypoglycemia.

New, rapidly acting insulin products, however, are not without potential problems:
a) the insulin analogue, as a new molecular entity, may have undesirable properties that are independent of its glucose lowering capabilities,
b) a short acting insulin might give rise to late, post-prandial hyperglycemia, and
c) rapid acting insulins might not be tolerated by diabetics with cardiovascular and/or neuropathic problems.

The sponsor submitted three, open-label, active-control, pivotal trials for review (035 conducted in IDDM patients from Europe, 036 conducted in IDDM patients from North America, and 037 conducted in NIDDM patients from North America). The sponsor presented HgbA1c data to establish probable non-inferiority for glycemic control, but was unable to present PK-PD data from the pivotal trials that would confirm the more rapid absorption and/or the rapid onset of action of X-14 compared to human regular insulin. The sponsor was encouraged to collected retinopathy data to help identify or exclude proliferative effects. The sponsor did collect retinopathy data on a subset of patients, but did not include it in the NDA submission. The sponsor was encouraged to identify patients with autonomic neuropathy to help identify or exclude aberrant responses to rapid changes in glucose levels. This was not done on a systematic basis. The importance of collecting data on the incidence of hyperglycemia-ketosis was discussed at the 2/96 Endocrine and Metabolic Advisory Committee meeting. This also was not done on a systematic basis. The open-label and active-control nature of the trial further limit the types of conclusions that can be drawn about these trials.

3. Objectives

The sponsor sought to optimize the glucose control that could be obtained with X-14. Three studies employed multiple shots of rapid acting insulins in conjunction with meals. To assess glucose control, the sponsor utilized measurements of HgbA1c and 8-point blood glucose profiles (self-collected glucometer readings). The glucose profile was designated as a major outcome parameter, but remains unvalidated.

4. CANDA submission.

There was no CANDA submission. A SAS data base was provided. Data were provided on two EXCEL spread sheets submitted in June 1999. (The hypoglycemia and HgbA1c data bases were not merged-limiting utility.) The data provided did not appear to be consistent with the data from the SAS data base.

5. Notable chemistry issues

The insulin is produced via recombinant DNA technology using the yeast S. cerevisiae. The technology is similar to that employed by the sponsor in production of other approved insulin products. [redacted]

The sponsor has provided documentation [redacted]

6. Notable pre-clinical studies

6.1. Growth promotion

Insulin and insulin-like growth factor I have a high degree of homology. Although promotion of growth is one of insulin's metabolic activities, IGF-I is more potent as a growth promoter. Changes in the insulin molecule could potentially alter its growth promotion properties. Growth promotion activity needs to be considered for several reasons:

a) The proliferative activity of IGF-I has been implicated as a mediator for some of the long-term complications of diabetes, e.g., retinopathy and nephropathy.
b) The clinical features observed with the hyperinsulinemia of severe insulin resistance states and Syndrome X have been attributed by some investigators to insulin's interaction with the IGF-I receptor.
c) The increased cardiac mass seen in acromegalic patients may not be tolerated by diabetic patients-particularly those with significant ischemic disease and elements of congestive failure.

In *in vitro* studies utilizing transfected BHK-cells with human insulin or human IGF-I receptors, the affinity of X-14 and one of its degradation products for the solubilized insulin receptor was slightly less than that of insulin. The affinity of X-14 and two of its degradation products for the solubilized IGF-I receptor was three magnitudes less than that of IGF-I, but somewhat greater (30-40%) than that observed with human insulin.

[redacted]

Dissociation studies were not performed. Thymidine uptake in several cell systems suggest that the mitogenicity of X-14 is similar to that of human insulin. Additional studies to assess the mitogenic potential of X-14 and ——— were performed using mammary cancer fibroblasts. Unfortunately, the results were inconclusive. The Ames test, mouse lymphoma assay, the unscheduled DNA repair assay in hepatocytes were negative for mutagenesis. The *in vivo* mouse micronuclei assay and the chromosome aberration test in cultured human lymphocytes were negative for clastogenesis.

The clinical significance for small differences in the IGF-I receptor binding is uncertain. Cumulative exposure may magnify the small differences observed in the *in vitro* assays, and diabetics often require insulin administration for decades.

In a one year toxicology studies in rats, the incidence of benign and malignant mammary gland tumors tended to be higher (p=0.06) in rats treated with X-14 versus human regular 100 U/kg/BID. The incidence of mammary tumors observed in another exploratory study with X-14 appears to be less than the incidence observed with ———— ——— (N.B. The affinity of ——— for the IGF-I receptor was 0.02% of IGF-I for the insulin receptor.)

6.2. Reproductive toxicity

In a pre- and post-natal study in rats were treated with insulin (placebo or X-14 [three doses] or human regular [one dose]) six days post-coitus to 20 days post-partum. Parent animals and offspring were sacrificed at 21 days post-partum. Renal dysplasia, predominantly on the right side, was more commonly found in rats treated with either X-14 or human regular insulin than in rats treated with sham placebo. The level of glycemic control for the animals was not provided. (See Safety results-Pregnancy.)

6.3. Electrocardiographic changes

Prolongation of QRS complex and QTc interval are the type of changes that have been associated with dysrhythmia and sudden death in human subjects. These changes appear to be related to the cellular alterations in the flux of glucose and/or potassium. Studies conducted by another sponsor with another insulin analogue suggest that such electrocardiographic changes could be induced transiently in dogs. (See review for NDA #20563.) The sponsor did conduct cardiovascular studies in nine cats. EKGs were done at −1 minute, +1 minute, and +19 minutes. The sponsor provided, however, only heart rate data; no QRS complex change data or QTc interval data were found in the appendices.

7. Notable pharmacokinetic-pharmacodynamic issues

7.1.Absorption-serum levels

In pharmacokinetic studies, the sponsor is expected to demonstrate absorption of the drug. In this case specifically, the sponsor has claimed that the engineered changes in their insulin molecule would increase the rate of absorption. This has been adequately demonstrated in non-obese, healthy volunteers (n=24) in a randomized, cross-over trial. The time-to-peak insulin level was 40 minutes for X-14 and 120 minutes for regular

human insulin. The sponsor also demonstrated in healthy volunteers that the median time to peak insulin levels were similar for X-14 and another insulin analogue, lispro.

In patients with diabetes, insulin values cannot be measured directly because most patients with any significant exogenous insulin exposure have anti-insulin antibodies in the serum. These must be removed to reduce interference [redacted] assays. These extractions were appropriately performed so that free insulin levels could be determined. The sponsor also assessed absorption of X-14 and regular in Type 1 patients given a "standard meal". The t-max for X-14 given immediately before the meal was 39.1 minutes; the t-max for human regular given 30 minutes prior to the meal was 55.2 minutes after the meal. The sponsor did not adequately assess the pharmacokinetics of Type 2 patients. (See Biopharm review.)

The AUCs of X-14 and human insulin injected subcutaneously appear to be comparable in normal volunteers (n=24). Although the AUC for X-14 is 6461+/-1207 and the AUC for human regular is 4669+/-836, the sample collection for the AUC determination was done over only six hours, and it is known that human regular insulin may still be absorbed beyond this time-point.

[redacted]

Pigs given equi-molar doses of insulin (0.025 U/kg) IV showed Cmax and clearance values for X-14 and human regular insulin respectively of 360 pM and 0.019 l/kg versus 456 pM and 0.021 l/kg. (The study was limited by the absence of an assay that could distinguish between the two insulins.)

7.2. Absorption: inter-patient/intra-patient variability

Inter-subject variation for pharmacologic agents is important for compounds that are not titrated Intra-subject variability, however, is of much more importance for compounds that are titrated in the individual patient. Intra-patient variability helps the physician determine whether changes in glucose despite similar dosing with insulin can be attributed to the insulin or to other factors. In a glucose clamp study done in non-obese, healthy men (n=18), the intra-patient variability for $C\text{-}max_{(insulin)}$ was extensive $sigma^2$=822 whereas the intra-patient variability for $Cmax_{(insulin)}$ was limited for human regular insulin; $sigma^2$=67.4 The differences in intra-patient variability for the other PK parameters were insignificant. If the $C\text{-}max_{(insulin)}$ correlates with $C\text{-}min_{(glucose)}$ and the $C\text{-}max_{(insulin)}$ is highly variable, it may be difficult for patients and physicians to determine a dose of X-14 that provides consistent glycemic control without wide swings blood glucose. The inter-subject variability for $C\text{-}max_{(insulin)}$ was greater for human insulin, $sigma^2$=24.02, than X-14, $sigma^2$=2.97, but the clinical significance of this type of variability is much less important than that of intra-patient variability. Non-parametric

assessment of t-max shows that that the intra-subject variability is less with X-14. These data suggest that, for the individual patient, the time-to-peak insulin value is less variable with X-14, but that the magnitude of that peak is more variable with X-14. This suggests that patients/physicians will be able to predict the time of action onset, but may not be able to predict the magnitude of the response to the insulin.

7.3. Variables influencing absorption

7.3.1. Injection site

The injection site is known to affect the rate of insulin absorption. Absorption from the abdomen is generally most rapid and consistent. Absorption from the extremities (deltoid or thigh) is more variable. Exercise and temperature can influence the rate of absorption at these sites. X-14 insulin and human regular insulin were given to resting, normal volunteers (n=18) at each site via subcutaneous injection in a 6-way cross-over study. The time to 50% AUC was more rapid for X-14 than regular human insulin regardless of the site selected. There were absorption differences by site for X-14. Although peak insulin levels were reached at a similar time regardless of site, the C-max was highest for the abdominal site. The C-max for the deltoid site was only slightly blunted, whereas the C-max for the femoral site was even further attenuated. At t=100 minutes, X-14 insulin levels from the abdominal site were higher than levels from the deltoid site and especially the femoral site. At t=200 minutes, X-14 insulin levels from the abdominal site were lower than levels from the deltoid site and femoral site.

7.3.2. Weight/thickness of SQ tissue-skin

No PK-PD studies were conducted to assess the effect of weight or skin-SQ thickness at the injection site. The importance of the latter is suggested by differential PK-PD findings by animal species and, more importantly, the absence of difference in the blood glucose profile by treatment in NIDDM patients. The more rapid onset of absorption and subsequent action of X-14 compared to human regular could not be demonstrated in rats and dogs, but could be shown in pigs, which have a skin thickness and structure more similar to human subjects.

The blood glucose profile data in NIDDM patients, although severely compromised by self-collection via glucose meters, showed glucose control with X-14 to be lower at only two of the eight time-points. The differences were less than 17 mg/dl. The NIDDM patients were modestly overweight. The mean BMI for patients exceeded 29 kg/m2; the mean weight exceeded 85 kg (~12 kg more than their IDDM counterparts). Anthropometric measurement of skin sites were not obtained in these patients. The dissociation and absorption may be optimal when the skin-subcutaneous tissue are at an intermediate thickness. Curiously, a post hoc analysis of the 90 minute post-breakfast glucose values in Study 035 patients who weighed at least 10 kg more than the mean weight for their gender had a higher 90 minute blood glucose than those who weighed at least 10 kg less if they were male or if they were female and using human regular. (See figures 1 and 2.) A similar analysis of the 90 minute post breakfast glucose minus the fasting glucose showed an increase by weight in males who used X-14 and a decrease in females who used X-14. There was no change in the glucose lowering effect by weight for those who

used human regular. (See figures 3 and 4.) A similar analysis of HgbA1c showed a small decrease by weight in men who used X-14. In men who used human regular and in women who used either human regular or X-14 insulin, there was an increase. (See figures 5 and 6.)

7.3.3. Effect of smoking

Smoking is thought to have an effect on insulin absorption. In part, this may be related to the vasoconstriction that occurs with nicotine exposure. This hypothesis was not formally evaluated by the sponsor. (Koivisto VA. Various influences on insulin absorption. Neth J. Med. 1985;28(Suppl.):25.) No PK-PD studies were done to asses this variable.

7.3.4. Drug concentration

Changing the concentration of the insulin suspension may facilitate the onset of insulin action. More dilute solutions (U10 and U40) are absorbed more quickly than the more concentrated forms (U100 and U500). (Heinemann L, et al. Pharmacokinetics and pharmacodynamics of subcutaneously administered U40 and U100 formulations of regular human insulin. Diabete Metab. 1992;18:21.) These more dilute formulations have PK-PD profiles comparable to the modified insulin analogues. [redacted] The sponsor has designed an insulin with rapid action at the U100 concentration.

7.3.5. Mixing with other insulins

The sponsor assessed the effect of mixing X-14 with NPH in 28 normal volunteers. The mixtures were injected immediately after mixing. Both C-max and t-max were blunted (6-29%), but the overall bioavailability was unchanged. The increase in the NPH peak would be consistent with the establishment of a new equilibrium between the various insulin species. The sponsor did not assess the effect of time between mixing and injection on the rate of absorption and the onset of action. It is possible that absorption kinetics could be significantly altered if the mixing was done significantly prior to the time of injection.

The sponsor did not assess the effect of mixing with other insulins including Velosulin, regular human insulin, ultralente, and lente.

The pivotal clinical trials were conducted with pens containing the rapid acting insulin (human regular insulin or X-14) and vials containing NPH. This precluded mixing.

8. Study design

8.1. General

The sponsor planned three parallel, open-label, active-control (with human regular insulin), pivotal studies in adult diabetics. Patients were to be screened and then entered into a four week, run-in period to optimize glucose control with human regular insulin dosed with meals and basal insulin. The run-in period could be extended if another dose of basal insulin was added. Patients were then randomized to six months of treatment

with X-14 or human regular insulin (2:1 in Studies 035 and 036: 1:1 in Study 037). IDDM patients could enter an extension study.

Table 1
Design features of clinical studies

Study	Diabetes Type	Study Type	Dosing Rapid Insulin	Basal Insulin	Dosing Basal Insulin	Tx Arm Duration	Blinding	Uniform Meal Challenge	Glucose Measures
035	1	parallel	with meals	NPH	1-2 shots	6 months	no	no	glucometer
036	1	parallel	with meals	NPH	1-2 shots	6 months	no	no	glucometer
037	2	parallel	with meals	NPH	1-2 shots	6 months	no	no	glucometer

Tx=treatment

Some patients were treated periods of time outside the protocol. Because glucose control depends, in part, on experience with the proper insulin regimen, alterations in the time intervals for physician-patient interaction and the time to titrate could be expected to alter outcome. In an open-label trial, there is more potential for imbalance in the respective treatment arms. The sponsor was asked to provide data on patients who fell outside the protocol. (It should also be noted that even with-in the protocol, differences in the duration of treatment could be up to 22 days.) The sponsor did not provide data for the three to six month interval. Inspection of the data suggest that, in the European study (035), proportionately more patients treated with X-14 were treated for excessively long periods. The numbers, however, were not sufficient to significantly alter the efficacy results. This imbalance was not seen in the other studies.

Table 2
Patients who were treated for periods of time outside the protocol

		Run-in (4 weeks)		0-3 months		0-6 months	
		Too short	Too long	Too short	Too long	Too short	Too long
Study 035	*HR*	5 (16 days)	14 (45 days)	14 (67 days)	14 (124 days)	10 (167 days)	10 (209 days)
	X-14	11 (10 days)	28 (44 days)	23 (69 days)	19 (122 days)	19 (168 days)	31 (225 days)
Study 036	*HR*	0 (NA)	14 (43 days)	3 (72 days)	7 (131 days)	6 (167 days)	10 (207 days)
	X-14	0 (NA)	26 (38 days)	7 (76 days)	7 (131 days)	14 (162 days)	21 (219 days)
Study 037	*HR*	1 (18 days)	3 (44 days)	1 (79 days)	0 (NA)	5 (167 days)	4 (197 days)
	X-14	0 (NA)	4 (39 days)	1 (79 days)	2 (113 days)	7 (164 days)	3 (198 days)

8.2. Patient selection criteria
8.2.1. Inclusion criteria
-duration of diabetes ≥24 months
-treatment with insulin ≥12 months
-≥18 years (≥35 years for Study 037)
-able to monitor glucometer
-able to take multiple insulin shots

8.2.2. Exclusionary criteria
-poor glycemic control, HgbA1c >11%
-recurrent severe hypoglycemia (no set criteria)
-active proliferative retinopathy
-cardiac disease (NYHA Class 3 or 4, unstable angina, MI within prior 12 months)
-renal dysfunction (serum creatinine ≥150 mmol/L [1.7 mg/dl])
-hepatic dysfunction (ALAT ≥2x ULN, alkaline phosphatase ≥2x ULN)
-severe hypertension (supine systolic BP ≥180 mmHg, diastolic ≥110 mmHg)
(supine diastolic BP >105 mmHg for Study 037)
-obesity, >35 kg/m^2 (>40 kg/m^2 for Study 037)
-insulin resistance (use of corticosteroids, insulin dose ≥1.4 U/kg)
-insulin or excipient allergy
-pregnancy or risk of pregnancy, lactation
-substance abuse

8.3. Number of patients
8.3.1. Disposition of patients before randomization

Table 3
Disposition of patients before randomization

Study	*Screened*	*Failed screening*	*Withdrew b/f run-in*	*Withdrew (run-in)*	*Withdrawal (run-in) b/c of AE*
035	1237	137	0	40	not indicated
036	1102	166	1 w MI, 1 w DKA	52	4 (1 w exacerbation-ulcerative colitis)
037	252	61-45 failed	15 withdrew consent 5 other	9	2

b f=before b/c=because w=with MI=myocardial infarction DKA=diabetic ketoacidosis

8.3.2. Disposition of patients after randomization

Table 4
Disposition of patients after randomization

Study	*Randomized*	*No drug exposure*	*No data post baseline*	*Per protocol*	*ITT**	*Completer*
035	1070	5	18	1006	1047	1011
036	884	2	16	803	866	815
037	182	0	5	156	177	170

*The sponsor defined intent-to-treat (ITT) as those exposed to drug AND with efficacy information beyond baseline. This would exclude patients who did not make it to the 3 month visit.

In Study 035, the withdrawal rate was similar except for the first month when proportionately more patients assigned to human regular insulin withdrew early. Of the patients treated with X-14, four withdrew for hypoglycemia, eight withdrew for ineffective therapy-dissatisfaction with therapy (five after the first month, one as late as 109 days), and one withdrew for ketosis. Of the patients treated with human regular

insulin, two withdrew for hypoglycemia, and five withdrew for ineffective therapy-dissatisfaction with therapy (one after the first month).

In Study 036, there was no disproportionate early withdrawal. Of the patients treated with X-14, none withdrew for hypoglycemia, three withdrew for ineffective therapy-dissatisfaction with therapy (all after the first month, one as late as 122 days), and none withdrew for ketosis. Of the patients treated with human regular insulin, none withdrew for hypoglycemia, and one withdrew for ineffective therapy-dissatisfaction with therapy within the first month.

In Study 037, there was no disproportionate early withdrawal. No patients withdrew for hypoglycemia or hyperglycemia.

There was some tendency for patients treated with X-14 to discontinue for lack of efficacy much later than patients treated with human regular insulin. The numbers of patients are not sufficient to significantly alter results.

8.4. Characteristics of the study population

The intended target population for the pivotal trials were adult diabetics who had established diabetes and were comfortable with intensive therapy/multi-shot insulin regimens.

8.4.1. Age

Of the 2129 patients exposed to trial drug product (X-14 or human regular insulin), none were minors (<18 years of age), and only 35 were older than 65 years of age.

8.4.2. Gender

Of the 2129 patients exposed to trial drug product, 1156 (54%) were male and 973 (46%) were female. There were relatively more males randomized in each of the three studies. There was no gender maldistribution in the treatment groups.

8.4.3. Race

Of the 2129 patients exposed to trial drug product, 2018 (95%) were classified as Caucasian, 36 (1.7%) as Black, 12 (0.6%) as Asian, and 63 (2.9%) as other . Only 10 of the minorities were enrolled in the European Study (035).

8.4.4. Location

Study 035 was conducted in Denmark (5 sites), Finland (4 sites), Germany (36 sites), Norway (5 sites), Sweden (5 sites), and the United Kingdom (33 sites). Study 036 was conducted in the United States and in Canada. Study 037 was conducted entirely in the United States.

8.4.5. Body mass index (BMI)

Approximately 50% of the IDDM patients exposed to drug product had a BMI ≥ 25 kg/m^2. There was no difference in the European and North American populations.

Approximately 60-65% of the NIDDM patients exposed to drug product had a BMI ≥25 kg/m^2.

8.4.6. Duration of diabetes

The majority of patients (both IDDM and NIDDM) were known to have had diabetes for more than 10 years. Although such patients are at increased risk for diabetic complications, the trial data may not represent the experience that the generalized population with long-standing diabetes could be expected to have because of the strict exclusion criteria, i.e., patients with active, proliferative retinopathy, elevated serum creatinine levels, significant cardiac disease, and problematic hypoglycemia (perhaps secondary to autonomic neuropathy) were excluded from the trials.

Table 5
Duration of Diabetes (yrs)

	Study 035		*Study 036*		*Study 037*	
	HR	*X-14*	*HR*	*X-14*	*HR*	*X-14*
Mean	15.0	14.7	15.8	15.7	12.9	12.7
Median	13.1	12.6	14.6	14.4	11.1	10.5
Min—Max						

8.5. Number of patients per investigator

An investigator is more likely to recognize associations between a drug and adverse reactions if the investigator has treated a sufficient number of patients with the compound for a sufficient duration. Individual investigator impact cannot be properly assessed when an investigator has treated fewer than ten patients in each treatment arm. The average number of patients per investigator was less than 20: 13 for Study 035, 15.2 for Study 036, and 10.7 for Study 037.

8.6. Blinding information

8.6.1. Blinding status

All three pivotal trials were open-label.

8.6.2. Rationale for open-label status.

The insulins had different pharmacokinetic profiles so the Sponsor wanted to give each insulin its optimal time.

8.6.3. Comments on the open-label design

Blinding is an important feature of study design. The ideal study would have utilized blinding with doses of the test insulin and placebo at the optimal time of action for each insulin species: 30 minutes before meals for human regular insulin and 5 minutes before meals for X-14. This design is significantly more cumbersome, but could have reduced some of the confounding present in the trials. If an open-label design is utilized, significant care must be taken to avoid test parameters that are subjective and to maintain high expectations for both treatment groups. None of the three pivotal trials was blinded.

Patients in these trials collected their own glucose profiles on glucometers which are known to have significant intrinsic and operator associated errors. Even with glucometers that have memories and can be down-loaded, there is no guarantee that the patient performed the measurements at the designated times and that the meals and the glucose values from the three glucose profile collection days were representative. (See the section on inability to validate glucose profiles.) Collection of hypoglycemia data is another example of a test parameter with elements of subjectivity. Patients were encouraged to report any episodes of suspected hypoglycemia even without documentation of glucose level. (Please see the hypoglycemia section regarding incomplete documentation.) Vasodilatory episodes and other events-particularly in the presence of autonomic neuropathy-could be perceived as hypoglycemia. The drug development literature listed reduced post-prandial hypoglycemia as a potential, and even, likely benefit. For more subjective episodes of hypoglycemia, there was the potential for an imbalance in reporting by patients. There was also the potential for physicians to be more aggressive with therapy (resulting in lower HgbA1c values), at least initially, if they perceived the hypoglycemia risk to be lower.

8.7. Controls

8.7.1. Control status

An active-control was employed. The control was human regular insulin.

8.7.2. Rationale for active-control

An active-control was employed because of an absolute requirement for insulin in IDDM patients.

8.7.3. Comments on active controls

The use of an active-control can present problems-particularly in an open-label trial. Equivalence can be more easily and (perhaps erroneously) demonstrated if strict attention is not given to optimizing the control group. (Spilker B. Chapter 94. Interpreting data from active medicine control groups. From Guide to Clinical Trials; 1991, Raven Press, New York.) HgbA1c values for human regular insulin treated patients essentially remained unchanged in the IDDM studies (035 and 036). They improved slightly for the NIDDM patients (037).

Confidence intervals may be more appropriate statistical measures when active controls are employed. (Rosner B. Chapter 7 from Fundamentals of Biostatistics; 1986, PWS Publishers, Boston.) Even these measures, however, may be problematic in an open-label trial.

8.8. Study drug information

X-14 has the empirical formula $C_{26}H_{381}N_{65}O_{79}S_6$. The primary structure is identical to that of human insulin except for the substitution of proline with aspartate in the 28th position of the B-chain.

Each milliliter of the commercial formula contains insulin X-14 (————, 100 U), glycerin (16 mg), phenol (1.50 mg), meta-cresol (1.72 mg), zinc (19.6 ug), sodium chloride (0.58 mg), and ———————— . disodium hydrogen phosphate dihydrate (1.25 mg) to a pH of 7.40.

[ ]

8.9. Dose-route-regimen

8.9.1. Subcutaneous injection

The pivotal trials were all conducted using only subcutaneous administration.

[ ]

[ ]

8.9.4. Site of injection

As discussed previously, the site of injection will influence the rate of absorption. In all trials, the recommended sites for the rapid acting insulin and the NPH were the abdomen and thigh respectively. If another site was used, it was not to be changed during the trial. The sponsor did not present any data on injection sites so it could not be determined if there was any imbalance in injection site by treatment group.

8.9.5. Regimens

8.9.5.1. Use of longer acting insulin

The trials were designed so that the rapid acting insulin (X-4 or regular human) would be given in conjunction with meals. Only NPH was to be employed as a basal insulin. During the course of the trials, the amount of insulin was increased for all treatment arms except the human regular arm in Study 036. Most of the increase could be attributed to an increase in the amount long-acting insulin. These changes were statistically different in Studies 035 and 036. (See Statistical review.)

Table 6
Amount of basal insulin (U/kg)

	Human regular			*X-14*		
	Baseline	*6 months*	*Change*	*Baseline*	*6 months*	*Change*
Study 035	0.29	0.29	0.00	0.29	0.32	0.03
Study 036	0.25	0.28	0.03	0.24	0.29	0.05
Study 037	0.22	0.25	0.03	0.23	0.27	0.04

8.9.5.2. Number and timing of injections

The number and timing of rapid and basal insulin doses can be modified to maximize glycemic control and minimize hypoglycemia. The open-label nature of the trial could lead to an imbalance in the number and timing of injections, and perhaps, the efficacy. Even though the timing and number of basal injections were not to be changed after the run-in period, this was done. A disproportionate patients treated with X-14 had an additional had an extra injection of basal insulin added to their regimen. The sponsor did not provide the actual number and timing of injections actually used, but the data suggest that some patients were receiving more than four or five shots per day and that some patients were receiving rapid-acting insulin at night. These data were requested.

Table 7
Basal insulin (NPH) time of administration or number of doses changed.

	1 injection deleted	*1 injection added*	*2 injections added*	*Injection time changed*
Study 035 HR	6	3	0	8
X-14	5	37	0	13
035 HR (run-in)	9	18	0	9
X-14 (run-in)	20	37	1	13
Study 036 HR	0	9	0	2
X-14	1	18	0	4
HR (run-in)	1	168	7	21
X-14 (run-in)	0	337	13 (+1-3 injections)	38
Study 037 HR	0	2	0	0
X-14	0	1	0	0
037 HR (run-in)	2	53	2	4
X-14 (run-in)	0	42	3	7

8.9.5.3. Mixing insulin

The pharmacokinetic profile of X-14 is altered when it is mixed with NPH from NovoNordisk. The degree of attenuation of C-max (~20%) and t-max (~10%) is modest if the mixing is done immediately before injection. In the clinical trials, there was no mixing because the rapid acting insulin was delivered by pens and the NPH via syringes.

8.10. Duration of therapy

All three pivotal trials were parallel trials in which patients were treated with X-14 or human regular insulin for six months. Patients with IDDM were also permitted to

extension trials: 036-extension and 050. Patients were maintained on the same therapy as in pivotal trials for at least another six months. (Preliminary data from 036 were presented. Data from 050 were not included.)

8.11. Concomitant medications
8.11.1. Other insulin products
Only NovoNordisk NPH was to be used. It was not mixed with the rapid acting insulin.

8.11.2. Beta blockers
Beta blockers are known to mask the signs of hypoglycemia. The sponsor did do an assessment of hypoglycemic-like events with the use of various medications. The assessment did not include beta-blockers. The sponsor did not do an assessment of hypoglycemic awareness and beta-blockers. Data on the frequency on the use of beta-blockers was not included in the NDA report. (See safety update.)

8.11.3. Drugs altering potassium status; drugs dependent on the kalemic state.
There were no drug interaction studies for patients using diuretics, potassium supplementation, or digoxin-related compounds. There were no adequate electrophysiologic studies in patients at risk for the EKG changes described previously. (See safety results.)

8.11.4. Glucocorticoids
Inspection of the drug interaction data indicate that patients using glucorticoids were included in the study despite protocol rules. There was no indication as to whether there was an imbalance in the treatment arm. There was no drug interaction assessment for hyperglycemia, the more expected event-although there was a drug interaction assessment for hypoglycemia.

8.12. Safety variables
8.12.1. Physical assessment
Physical exams with weights were performed during screening, at visit 3 (t=0), at visit 7 (t=3 months), and at visit 10 (6 months)/endpoint. Vital signs were obtained at each visit. Funduscopy was to be performed at baseline, but it was not specified whether the exams were to be conducted by an ophthalmologist and whether the exam was to be a dilated exam. The sponsor obtained baseline and follow-up retinal films for a subset of patients, but did not indicate how the subset was selected. The sponsor has not yet submitted the data. They indicated that the pairs of retinal films could not easily be assessed by a single reader because they had been obtained at different sites that used a variety of techniques.

Because of potential concerns regarding intolerance of rapid changes in glucose levels in patients with autonomic neuropathy, the sponsor was asked to systematically evaluate patients for sensory and autonomic neuropathy using the standard examination modalities for proprioception, vibratory sense, and fine-touch/pressure (monofilament) as well as concomitant orthostatic blood pressure-heart rate assessment and R-R intervals on a rhythm strip (in conjunction with the EKG.) These elements of routine diabetes care were not performed as part of the studies.

8.12.2. Laboratory assessment

8.12.2.1. Routine assessments

The trials were designed to collect routine clinical chemistry tests, lipids, routine hematologic tests, and urine assessment by dipstick. The dipstick assessments were reportedly performed at each visit. The other clinical chemistry and hematology laboratory studies were to be performed at t=0, 3 months, and 6 months/endpoint. Presumably the clinical chemistry studies were obtained in the fasting state-although this was not explicitly stated. Otherwise, the triglyceride values would not be interpretable. It should be noted that the sponsor did not present absolute triglyceride values, but rather a change from baseline. The clinical chemistry assessment reports listed all of the routine assessments-except glucose. (A fasting glucose would have been a useful corroborative parameter.)

8.12.2.2. Antibodies

Samples for antibodies specific to human regular insulin and X-14 insulin analogue were assessed at baseline and at 6 months (and at 3 months in 036 and 037). Antibodies were not obtained from 1 site in Study 036, (154-637; n=7). Samples for antibodies cross-reactant to both types of insulin were obtained on a similar schedule (despite the listing in Table 4-2 in volume 93). Some samples for cross-reactant antibodies were obtained during the 036 extension trial.

8.12.3. Electrocardiographic assessment

Electrocardiograms were obtained at baseline and at 6 months/endpoint. These electrocardiographic studies were not scheduled to permit assessment of potential transient changes in QTc intervals post dosing. The electrocardiograms also did not include rhythm strips for more accurate assessment of R-R intervals that would permit identification of diabetics with autonomic neuropathy.

8.13. Efficacy variables

HgbA1c-at baseline, 3 months, and 6 months

-HPLC assay performed at [redacted]

8-point blood glucose profiles-at baseline, 5 months, and 6 months

-performed over the course of one week day

-performed before meals, 90 minutes post meals, at bedtime, and at 2 A.M.

-via self-measurements using the [redacted] meter

8.14. Procedures

Unblinded patients were to collect 8-point blood glucose profiles using a glucose meter. (See efficacy variables.) There were no standardized meals. There were no food diaries. During the extension trial, to help validate the 8-point profiles, a subset of subjects were asked to consume a Sustacal meal with caloric content similar to that of their individual, routine meals. Blood samples were obtained at ten time-points over the next 4.5 hours.

Venous samples were sent to the lab for analysis. It is unclear as to whether the samples used for the concomitant glucometer readings were taken from the venous samples or separate fingersticks and whether the patients did the readings themselves on their own meters.

Patients were also asked to undergo funduscopic exams. A subset of patients underwent retinal photography at baseline and six months/endpoint.

8.15. Protocol amendments/administrative changes

Study 035

10/22/96- 1) The sponsor intended to delete the extension study and then rescinded their decision.

4/8/96- 1) Only hypoglycemic episodes with symptoms were to be recorded.
2) Samples for cross-reactive antibodies were to be collected in addition to the insulin specific antibodies.
3) Non-serious adverse events were to be followed to the last visit.
4) The investigator was to determine which abnormal laboratory studies were to be listed as adverse events.
5) The time and type of last insulin injection prior to a hypoglycemic episode was to be recorded (in part, because of the differences in meal patterns throughout Europe).

10/27/96- 1) Reportedly minor changes.

10/30/96- 1) Norway: Reportedly minor changes.

11/27/96- 1) Reportedly minor changes.

11/28/96- 1) Austria, Germany, Switzerland: QOL studies were permitted.

12/2/96- 1) United Kingdom: Reportedly minor changes.

12/18/96- 1) Specified windows for EKGs and funduscopic exams.

12/18/96- 1) Denmark: Depo-contraceptives were permitted and barrier methods were excluded.

1/15/97- 1) Permitted funduscopic exams to replace retinal photos.

1/20/97- 1) Sweden: Reportedly minor changes.

6/20/97- 1) Sweden: Reportedly minor changes.

6/23/97- 1) Austria, Germany, Switzerland: Reportedly minor changes.

7/30/97- 1) Austria, Germany, Switzerland: Reportedly minor changes.

8/18/97- 1) United Kingdom: Reportedly minor changes.

11/14/97- 1) United Kingdom: Reportedly minor changes.

Study 036

11/25/96-1) The sponsor changed the definition of hypoglycemia to:
Mild-having symptoms of hypoglycemia and/or a glucometer reading <45 mg/dl. Major-symptoms including impaired consciousness that required intervention from a third party and hospitalization. The degree of intervention would be recorded. (The sponsor was informed that this was still not consistent with requested definition.)
2) CRFs would be provided by [redacted]
3) The definition of specific adequate contraceptive measures was deleted.

2/24/97- 1) Antibody measurement at three months were added.
4/1/97 - 1) The run-in period was to be four weeks +/-three days unless an additional shot of basal insulin was added at breakfast (at investigator discretion). To make sure that the patient was stable on the changed dose for one week, the run-in period could be increased by one week. The number and timing of NPH injections was not to be changed after randomization, t=0.

Study 037
12/20/96-) The sponsor changed the definition of hypoglycemia to:
Mild-having symptoms of hypoglycemia and/or a glucometer reading <45 mg/dl. Major-symptoms including impaired consciousness that required intervention from a third party and hospitalization. The degree of intervention would be recorded. (The sponsor was informed that this was still not consistent with requested definition.)
2) CRFs would be provided by [redacted]
3) The definition of specific adequate contraceptive measures was deleted.
12/30/96-1) The provision [redacted] was deleted.
2/24/97- 1) Antibody measurement at three months were added.
3/26/97- 1) The allowable BMI was increased from 35 to $\leq$40 kg/m^2.
(Some heavier patients were recruited prior to this amendment.)
4/1/97 - 1) The run-in period was to be four weeks +/-three days unless an additional shot of basal insulin was added at breakfast (at investigator discretion). To make sure that the patient was stable on the changed dose for one week, the run-in period could be increased by one week. The number and timing of NPH injections was not to be changed after randomization, t=0.

8.16. Statistical analysis
8.16.1. Hypothesis
The sponsor hypothesized that the glycemic control (HgbA1c) achieved by patients using X-14 would not be inferior to the glycemic control in patients using human regular insulin when adjustments for hypoglycemia were made. (The sponsor later wished to claim superiority.)

8.16.2. Interim analysis
No interim analyses were planned or conducted.

8.17. Inspections
Inspections were conducted at several site in North America. One site (165) for Study 036 was found to be problem free. One site (188) for Studies 036 and 037 was found to have minor violations. Another site (137, 159) for Study 036 was found to have violations including the failure to report adverse events.

[redacted] The data from this site (n=19) are not reliable. The numbers were not sufficient to significantly alter the conclusions.

9. Efficacy Results
9.1. Efficacy variables
9.1.1. Glucose parameters
Integrated glucose control is best measured by HgbA1c. It is the standard that is accepted by the F.D.A. and the academic community. The Diabetes Control and Complications Trial (DCCT) has shown that lower HgbA1c levels obtained with intensive insulin therapy in IDDM patients were associated with fewer complications than the higher levels of HgbA1c associated with conventional therapy. Data from the United Kingdom Prospective Diabetes Study (UKPDS) supports this same relationship between HgbA1c level and complication rate for NIDDM patients. Whether these data can be extrapolated to modified insulins or other hypoglycemic agents-which may have other growth potentiating and metabolic properties is not yet known. Nonetheless, HgbA1c appears to be the most appropriate outcome variable-given our current state of knowledge.

The clinical significance of other post-prandial parameters is more dubious. The oral glucose tolerance test, which uses oral liquid glucose (50, 75, or 100 gms), has been well validated. Vagaries in gastric emptying are not a confounding variable as they are in mixed meal testing. No normal values for post-prandial glucose have been established-even with the use of standardized meals. Furthermore, measurements of glucose at a single time-point, with the possible exception of fasting values, do little to help the clinician estimate the extent and duration of glucose exposure. The sponsor chose 90 minutes as the time to measure post-prandial glucose. When 90 minute post breakfast glucose values from Studies 035, 036, and 037 are plotted against concomitant HgbA1c values, there is no correlation regardless of treatment (X-14 or regular human insulin). (See figure 7.) The sponsor has also suggested that rapid glucose lowering is better because it is "more physiologic" and could provide better glucose control. When the most favorable glucose excursion (90 minute post breakfast glucose values minus fasting glucose values) from Studies 035, 036, and 037 is plotted against the respective HgbA1c, there is no correlation regardless of treatment (X-14 or regular human insulin). (See figure 8.) Similarly, when the change in the HgbA1c over the course of the study is plotted against the glucose excursion, there is no correlation regardless of treatment (X-14 or regular human insulin). (See figures 9.) The glucose excursion, however, can be used be used to describe an insulin's onset of action or glucodynamic profile.

9.2. Validity of data collection
The sponsor obtained the above glucose values during 8-point glucose profiles (fasting, 90 minutes post-prandial, at bedtime, and at 2 A.M.) during the pivotal trials. These measures were complicated by the use of glucometers and their limited accuracy, the lack of meal standardization in the parallel trials, and the dependence on self-collection in open-label trials. The sponsor provided no glucose measurements from a clinical laboratory.

In an attempt to validate the post-prandial glucose measurements and the glucose profile, the sponsor conducted a parallel, Sustacal challenge study on a subset of patients in the extension trial. Only patients from selected centers were invited to participate. 175

patients participated. It is unclear as to whether they were all tested at the same time, 12 months. Patients were not randomized to a treatment arm, rather they tested with the same insulin that they had used during the pivotal trial. Although Sustacal was used, the dose was not standardized. Patients were instructed to list a usual breakfast, which was then converted to a Sustacal equivalent in an unblinded setting. Patients were not dosed on U/kg basis. Rather, patients used their usual insulin doses. Samples for glucose were taken at 10 time-points over approximately 4.5 hours. Readings were also taken with glucometers at the same time-points. It is unclear as to whether patients did the readings or whether the laboratory did the readings.

The data provided by the sponsors does not support validation of the glucose measurements obtained during the pivotal trials. (See review prepared for the 3/31/99 submission to the NDA.) Inspection of the 10-point glucose profile (page 82) suggests that the fasting glucose was higher for patients on human regular insulin than for patients on X-14. This differs from the self-measured fasting glucose data obtained at six months (end of the pivotal trial) and suggests that the selected population may differ from the pivotal trial population. The relationship between the blood glucose and plasma glucose samples was not straight forward. Although blood glucose is typically lower than serum or plasma samples by approximately 11%, the sponsor's data suggested that such values were 20-30% lower, that the relationship was not linear, and that there were significant outliers (page 84). The sponsor did not provide any data on the predictive value or precision of the given blood glucose meter readings. The sponsor reported that the mean 10-point plasma glucose profiles did not "agree" with the 8-point meter blood glucose profiles. Whether changes in glycemic control over the course of the extension study contributed to this is unknown. The sponsor did not provide more data with the main body of the study report. Because the sponsor's blood glucose data could not be validated, they were not rigorously assessed for the NDA review. The absence of validated data severely limit that which can be claimed by the sponsor.

It should also be noted that inspection of the 10-point glucose profile (venous samples determined using a validated lab assay) suggests that there are limited differences between the two insulins. The error bars were not fully legible, but the SEM bars appeared to overlap the means. Furthermore, the magnitude of difference for the glucose values was small. The maximal difference was approximately 1 mmol/L or 18 mg/dl and persisted for less than 60 minutes.

9.3. Efficacy results

9.3.1. HgbA1c

Despite entry into clinical trials, the glycemic control of the patients in studies 035, 036, and 037 did not substantially improve and was less than optimal. Glycemic control was similar regardless of the treatment used. The HgbA1c $_{(>3 \text{ months of treatment})}$ and number of hypoglycemic-like episodes requiring intervention at equilibrium $_{(>3 \text{ months of treatment})}$/the number of patients ($_{>3 \text{ months of treatment}}$) were 7.98% and 63 events/343 persons (0.18) versus 7.86% and 119/688 (0.17) for human regular insulin and X-14 in Study 035 respectively. (N.B. There were discrepancies for the number of hypoglycemic events throughout the

submissions. See Hypoglycemia. These numbers were obtained from the statistician and the SAS data base.) The comparable values in Study 036 were 7.99% and 50 events/271 persons (0.18) versus 7.78% and 124 events/571 persons (0.22) for human regular insulin and X-14 respectively. It should be noted that there were 19 patients at a site whose data were found to be unreliable. Recalculation of the HgbA1c data indicates that the overall HgbA1c mean values remain unchanged. [See appendix.]) Finally, these outcome variables were 7.69% and 3 events/85 persons (0.035) versus 7.81% and 6 events/89 persons (0.067) for human regular insulin and X-14 respectively in Study 037. The largest difference between HgbA1c values in protocols that were open-label and utilized a non-inferiority hypothesis was observed in Study 036, was ~0.21% in favor of X-14. The hypoglycemia rate, however, was 22% higher. In the NIDDM study, the HgbA1c was minimally better for the human regular insulin patients, ~12%, with only half the hypoglycemia.

It should also be noted that patients treated with X-14 received more insulin per day (1-3 U) than did their human regular insulin counterparts. In addition, the number and timing of injections are maneuvers that can be used to optimize glycemic control and minimize hypoglycemia. The data suggest that injections were given outside the protocol. The potential for imbalance is greater in an unblinded study. The sponsor did not include information on the actual number of shots used and the timing of the shots. Lastly, even it patients followed protocol, the treatment period for patients could vary by up to 22 days. A longer treatment period would permit patients/physicians more time to optimize treatment regimens. It is not known whether there was any imbalance in the duration of treatment by treatment arm.

Table 8
Efficacy results 035 (IDDM-Europe)

		Treatment		
	Baseline	*Human regular*	*Baseline*	*X-14*
HgbA1c (%)	7.97 (n=346)	7.98 (n=340)	7.95 (n=697)	7.86 (n=682)
# Hypo-total		151 (n=358)		312* (n=707)
Mean hypos-total		0.42		0.44
Median hypos-total		0		0
# Discontinuations for hypo-total		2		4
Intervention w glucagon/IV glucose		25*		40*
Pt-no hypos-total		291		602
# Hypos/pts w hypos –total		2.25		2.97
#Hypos-end		63 (n=343)		119 (n=688)
Mean hypos-end		0.18		0.17
Median hypos-end		0		0
# Discontinuations for hypo-end		0		1
Intervention w glucagon/IV glucose		11		15
Pts-no hypos-end		304		638
Hypos/pts w hypos-end		1.62		2.38
Insulin dose-mean (U/g)	0.70 (n=349)	0.69 (n=343)	0.69 (n=698)	0.70 (n=685)
Insulin dose-median (U/kg)	0.68	0.68	0.67	0.69

*The number of hypoglycemic events for human regular was listed as 152 (Vol. 67, p117), 151 (Vol. 67, p118), and 151 (SAS data set). The number of events for human regular requiring IV glucose or glucagon was listed as 26 (Vol. 67, p117), 25 (Vol. 67, p118), and 25 (SAS data set).
The number of hypoglycemic events for X-14 was listed as 314 (Vol. 82, p117), 312 (Vol. 67, p118), and 312 (SAS data set). The number of events for human regular requiring IV glucose or glucagon was listed as 42 (Vol. 67, p117), 40 (Vol. 67, p118), and 40 (SAS data set).

Hypos=hypoglycemic-like reactions requiring intervention
Total=over the course of the entire study
End=over the last three months of the study

Table 9
Efficacy results 036 (IDDM-North America)

		Treatment		
	Baseline	Human regular	Baseline	X-14
HgbA1c (%)	7.97 (n=279)	7.99 (n=271)	7.90 (n=586)	7.78 (n=576)
# Hypo-total		155* (n=286)		265 (n=596)
Mean hypos-total		0.54		0.44
Median hypos-total		0		0
# Discontinuations for hypo-total		0		0
Intervention w glucagon/IV glucose		11		26
Pt-no hypos-total		231		491
# Hypos pts w hypos –total		2.82		2.52
#Hypos-end		50 (n=271)		124 (n=571)
Mean hypos-end		0.18		0.22
Median hypos-end		0		0
# Discontinuations for hypo-end		0		0
Intervention w glucagon/IV glucose		2		8
Pts-no hypos-end		249		519
Hypos pts w hypos-end		2.27		2.38
Insulin dose-mean (U/g)	0.68 (n=274)	0.69 (n=263)	0.66 (n=578)	0.71 (n=565)
Insulin dose-median (U/kg)	0.65	0.67	0.64	0.68

*The number of hypoglycemic events for human regular was listed as 157 (Vol. 82, p107), 155 (Vol. 82. p110). and 155 (SAS data set).
The number of hypoglycemic events for X-14 was listed as 266 (Vol. 82, p107), 265 (Vol. 82, p110), and 265 (SAS data set).

Table 10
Efficacy results 037 (NIDDM)

		Treatment		
	Baseline	Human regular	Baseline	X-14
HgbA1c (%)	7.82 (n=87)	7.69 (n=85)	8.13 (n=89)	7.81 (n=89)
# Hypo-total		8 (n=91)		12 (n=91)
Mean hypos-total		0.09		0.13
Median hypos-total		0		0
# Discontinuations for hypo-total		0		0
Intervention w glucagon/IV glucose		1		1
Pt-no hypos-total		86		82
# Hypos/pts w hypos –total		1.6 (n=5)		1.33 (n=9)
#Hypos-end		3 (n=85)		6 (n=89)
Mean hypos-end		0.035		0.067
Median hypos-end		0		0
# Discontinuations for hypo-end		0		0
Intervention w glucagon/IV glucose		1		1
Pts-no hypos-end		82		84
Hypos pts w hypos-end		1 (n=3)		1.2 (n=5)
Insulin dose-mean (U/g)	0.61 (n=87)	0.70 (n=84)	0.61 (n=88)	0.66 (n=87)
Insulin dose-median (U/kg)	0.56	0.60	0.55	0.62

9.3.2. Glucometer readings

The glucose profiles are based on self-collected readings with an imprecise instrument. The data collected could not be validated. In addition, not all patients provided data for all data points. The data point most frequently reported was the 2 A.M. value. Nonetheless, the data were inspected in a cursory fashion. The time-point with the maximal difference between X-14 and human regular insulin was at 90 minutes post breakfast. The differences for Studies 035, 036, and 037 were 1.1, 1.8, and 0.5 mmol/L (or 19.8, 32.4, or 9 mg/dl) respectively. The differences between X-14 and human regular insulin were smaller at the other time-points. Most patients were not hypoglycemic at night. The lowest mean value was 7.8 mmol/L (or 140 mg/dl). The profiles for the NIDDM patients do not support the hypothesis that X-14 has significantly more rapid onset in NIDDM patients. The means of the eight time-points were not appreciably different except for Study 036 and tended to support the absence of major differences in glycemic control, but the correlation of the mean glucose with the HgbA1c level was poor. The HgbA1c values were lowest in the Study 037, but the mean glucose values were highest!

Table 11

Blood glucose profiles (mmol/L) by study

	B/f breakfast	*90 min p breakfast*	*B/f lunch*	*90 min p lunch*	*B/f supper*	*90 min p supper*	*B/f bedtime*	*2 A.M.*
035								
HR	**7.7**	10.0	7.3	8.3	**7.2**	8.9	**8.5**	**7.8**
X-14	8.4	**8.9**	**7.1**	**7.9**	7.9	**8.3**	8.6	8.3
036								
HR	**8.7**	10.6	7.8	9.2	**8.0**	9.5	9.2	**8.7**
X-14	8.9	**8.8**	**7.0**	**7.7**	8.6	**8.5**	**9.1**	8.8
037								
HR	8.6	10.1	7.9	**8.6**	**7.9**	**9.0**	**9.2**	**8.6**
X-14	8.6	**9.6**	**7.0**	8.7	8.6	9.3	9.4	9.1

B/f=before min=minutes p=post

Table 12

Means of the 8-point glucose profile (mmol/L; mg/dl) by study

		Mean glucose profile	
		mmol/L	*mg/dl*
Study 035	Human regular insulin	8.21	147.8
	X-14	8.18	147.2
Study 036	Human regular insulin	8.96	161.3
	X-14	7.64	137.5
Study 037	Human regular insulin	8.74	157.3
	X-14	8.79	158.2

9.3.3.Lipids
The lipid parameters (HDL, triglycerides, and total cholesterol; presumably fasted levels) were not statistically or clinically different between the two treatment groups in the three studies.

9.3.4. Overall outcome
The clinical trials suggest that the levels of glycemic control as measured by HgbA1c were similar between the two treatment groups after adjustments for the numbers of hypoglycemic-like events requiring intervention from a third party (>3 to 6 months/endpoint). Higher insulin doses, many injections, and use of basal insulin-other than at bedtime were required to achieve the stated HgbA1c values. No comments can be made on fasting glucose values can because the sponsor did not obtain any laboratory validated values. The only glucose data, the glucose profiles, were obtained by unblinded patients using glucose meters. The sponsor was unable to validate these data. The glucose profiles, however, do suggest that the insulin may not have rapid onset in NIDDM patients. Although this insulin analogue may offer convenience, the altered PK-PD profile does not appear to offer true physiologic benefit. The correlation between HgbA1c and the 90 minute post-prandial glucose (breakfast) was negligible.

10. Safety results
10.1. Extent of exposure
Using very conservative estimates, there have been over 700 patient-years of experience with X-14 in the setting of controlled pivotal clinical trials. There is additional longitudinal experience from the extension trials.

10.2. Adverse events
10.2.1. Death
There were two deaths overall in the pivotal trials. There were two additional deaths in other trials. All were cardiovascular in nature, but there were no deaths that were clearly attributable to sudden death. The total number of deaths was small and likely reflects the direct and indirect exclusion criteria. The patients most at risk for severe dysrhythmias because of their underlying disease, e.g. active cardiac disease and problematic hypoglycemia (perhaps due to autonomic neuropathy), their use of drugs dependent on the kalemic state, e.g. digoxin, and their use of drugs that alter the kalemic state, e.g. diuretics. tended to be excluded from the trials. For the given patient population, there was no excess mortality in the X-14 treatment arm.

Table 13
Deaths during clinical trials

	Treatment	Study	Patient I.D.	Adverse event
Pivotal trials	X-14	035	1452	myocardial infarction
	Human regular	037	8129	myocardial infarction
Other trials	Human regular	050-ext	1181	CVA
	Human regular	064	8402	death during exercise
				"morbus arteriosclerosis cordis

10.2.2. Cardiac events

There were additional, non-fatal, cardiac events during the pivotal trials. Most of these occurred during the NIDDM study (037). There was no clear imbalance. Electrocardiograms were taken at baseline and at exit. Patients were categorized as having an normal or abnormal study and as to whether there was a change in that status. (See table 15 below.) Patients who had an abnormal baseline study and went on to have further changes were not identified, nor was the nature of the change tabulated. Inspection of the data listings revealed that the categorization of abnormal often did not have a description of the abnormality. These problems limited analysis. Inspection of the data listings (pre-treatment, baseline, ~180 days, and ~360 days) revealed that non-specific ST and/or T wave changes and sinus bradycardia were the most common findings. There were 23 reports of new bradycardia and one report of more profound bradycardia in the X-14 treated patients. There were nine such reports in patients treated with human regular insulin. The ratio of events X-14:Human regular was 2.7-some what greater than predicted by the ratio of patients exposed to drug: 1.9. The clinical significance of this finding remains unclear; none of the cardiac events have been linked to this phenomenon.

Table 14

Cardiac events during the pivotal trials

Treatment	*Study*	*Patient I.D.*	*Adverse event*
X-14	035	1452	myocardial infarction-death
X-14	036	6910	coronary artery disorder
X-14	037	8008	stenosis on cath→CABG→angioplasty
X-14	037	8125	myocardial infarction
X-14	037	8198	angina→cath→angioplasty
Human regular	035	0326	angina-2 episodes
Human regular	035	1283	sx→stenosis found→CABG 2 mo later
Human regular	036	6311	angina
Human regular	037	8129	myocardial infarction
Human regular	037	8028	myocardial infarction
Human regular	037	8005	coronary vasospasm
Human regular	037	8159	angina
Human regular	037	99092	atrial fib
Human regular	037	8129	myocardial infarction-death (after discontinuation)

N.B. The randomization was 2:1 in Studies 035 and 036. The randomization was 1:1 in Study 037.

Table 15

Changes in electrocardiographic findings

	X-14 (n=707)	*HR (n=358)*	*X-14 (n=596)*	*HR (n=286)*	*X-14 (n=91)*	*HR (n=91)*
Abnormal t=0/Abnormal 6 months	24	14	83	55	33	30
Normal t=0/Abnormal 6 months	16	4	56	29	8	6
Normal/abnormal t=0/Normal 6 months	643	323	431	185	48	48
Missing	24	17	26	17	2	7

HR=human regular

10.2.3. Other cardiac findings

In study 039, 17 healthy volunteers were given X-14 and human regular insulin over 2 hours in a cross-over fashion. The route of administration was IV. The onset of action, the precipitation of hypoglycemia, and the precipitation of any hypoglycemia-related EKG changes would no be expected to differ by compounds when administered this way. The design of the study does not address whether the more rapid onset of action or other factors contribute to electrocardiographic changes after subcutaneous dosing. The study does not assess the effects of hypokalemia or interactions with cardiac drugs that are affected by the kalemia state. (See the comments from the Cardio-Renal Division.)

10.2.4. Hypoglycemia

The definition of hypoglycemia for pharmaceutical trials needs to be more rigorous than the definition of hypoglycemia employed in clinical practice. The rationale for this includes the fact that glucose meters are not very accurate, patients may have vasodilatory episodes that mimic hypoglycemia, and many trials are open-label. The sponsor permitted patients to report hypoglycemia-even if they felt hypoglycemic and had no documentation. For this reason, the sponsor was asked to provide hypoglycemia rates according to the definition 36 mg/dl or requiring intervention from a third party. Unfortunately, the data were not provided in a timely manner and in a usable format. Therefore, the reviewer assessed the hypoglycemic-like events that required the intervention of another. The data supplied by the sponsor were internally inconsistent. (See footnote 1.) The data from the SAS data base were employed.

Many of the hypoglycemic events were poorly documented. The blood glucose level was twice as likely to be documented in patients using human regular insulin as opposed to those using. X-14. In addition, some events were not clearly hypoglycemic. Of the 119 X-14 associated hypoglycemic-like events during the last 3 months of Study 035, blood glucose levels were known for 27 events (23%). Blood glucose levels were $\leq$36 mg/dl in only 7 (6%) of these cases. Of the 63 comparable events with human regular, blood glucose levels were known for 33 events (52%). Blood glucose levels were $\leq$36 mg/dl in only 8 (13%) of these cases. Two patient treated with X-14 had glucose levels of 77 and 120 mg/dl respectively. Of the124 X-14 associated hypoglycemic-like events during the last 3 months of Study 036, blood glucose levels were known for 56 events (45%). Blood glucose levels were $\leq$36 mg/dl in only 34 (27%) of these cases. Of the 50 comparable events with human regular, blood glucose levels were known for 39 events (78%). Blood glucose levels were $\leq$36 mg/dl in only 5 (10%) of these cases. One patient treated with human regular had a glucose level of 180 mg/dl. The poor documentation does limit the validity of the data.

Because patients may experience hypoglycemia when they are being titrated on new dosing regimens, it is best to compare hypoglycemia rates after patients have reached some sort of steady state. Equilibrium hypoglycemia rates were determined from events that occurred during the last three months of the study. These three months also coincided with time over which HgbA1c reached it equilibrium. Indeed patients had 14-110% more hypoglycemia in the first three months of the study than in the last three months. The

HgbA1c $_{(\text{on drug } >3 \text{ months})}$ and number of hypoglycemic-like episodes requiring intervention$_{(\text{on drug } >3 \text{ months})}$/the number of patients ($_{\text{on drug } >3 \text{ months}}$) were 7.98% and 63 events/343 persons (0.18) versus 7.86% and 119/688 (0.17) for human regular insulin and X-14 in Study 035 respectively. In Study 036, the comparable values were 7.99% and 50 events/271 persons (0.18) versus 7.78% and 124 events/571 persons (0.22) for human regular insulin and X-14. Finally, these outcome variables were 7.69% and 3 events/85 persons (0.035) versus 7.81% and 6 events/89 persons (0.067) for human regular insulin and X-14 respectively in Study 037. The numbers of serious hypoglycemic events/person/year that would be expected in IDDM patients with a comparable HgbA1c (~8%) according to the DCCT is ~0.45. The rates in these studies were 50-60% higher. This may reflect the inclusion of poorly documented events and events that were not actually hypoglycemia.

It should be noted that the median number of hypoglycemic events for all the trials regardless of treatment was zero. This indicates that hypoglycemia was experienced by only a fraction of the trial populations. The number of events per person among those who had hypoglycemic events was similar except for Study 035 in which X-14 patients had ~64% more episodes per person than patients using human regular insulin. Patients with hypoglycemic episodes requiring intervention tended to be older than the respective population at large: Study 035: X-14 +0.9 year and Human regular +1.5; Study 036: X-14 +2.4 years and Human regular: +3.7 years.

When hypoglycemic events were normalized (total events=100 events) and then plotted over the course of the day, there were no clear patterns. Unlike the studies with lispro and human regular insulin in which the hypoglycemia that occurred at night was a small fraction of the overall numbers of hypoglycemic events, the hypoglycemic events for both X-14 and human regular insulin in these studies were more evenly distributed throughout the day. (See figures 10 and 11.) For nocturnal events, X-14 showed a tendency for relatively more events during the early evening whereas human regular insulin showed a tendency for more events during the later evening hours. The clinical significance of the temporal aspect of the events remains to be determined.

The sponsor did an assessment of hypoglycemic rates in patients using various medications and X-14 versus human regular insulin. (See safety update.) Curiously, the analysis did not include beta-blockers. For unclear reasons, X-14 patients using progestogens, some (but not all) types of penicillin, anti-infective agents for acne, and selective beta-2 adrenoceptor agonists had higher rates of hypoglycemia-like events requiring intervention than X-14 patients not using the particular medication and, in most cases, higher than the human regular insulin patients whether or not they used the concomitant medication in question. There are no readily apparent explanations for these observations.

Footnote 1
Study 036 The number of hypoglycemic events for human regular requiring intervention was listed as 152 (Vol. 67, p117), 151 (Vol. 67, p118), and 151 (SAS data set). The number of events for human regular